Down But Not Out

HIV-Impaired Immune Systems Might Be Able To Make a Comeback

By Mark Schoofs

"The central question," explained William Paul, director of the federal AIDS research program, "is this: Are we going to get immune reconstitution?" Paul was speaking between sessions at a high-powered AIDS science conference last week in Washington, D.C., where about 2000 doctors and researchers heard updates on the effectiveness of multi-drug cocktails. Usually involving a protease inhibitor, these regimens have been able to suppress HIV in many, though not all, patients.

Some scientists even think the virus could eventually be eradicated. Still, most are "pessimistic" that the battered immune system could regenerate, said Paul. "But for the first time, I've seen encouraging signs." Those signs were presented by French researcher Brigitte Autran, who observed three phases of immune system regeneration in eight patients. First, there is a rise in the number of immune cells—called CD4 T cells—that HIV infects. Next, after about two months of successful therapy, there is a general calming of the immune system, which has been locked in a feverish struggle with HIV since the moment of infection. These two phases have been noticed by other researchers. But what "astonished" Autran and kindled hope in Paul was a third phase.

To understand it, here's a crash course on the immune system. Each T cell is programmed to recognize only one germ: The T cell for hepatitis, for example, cannot recognize the virus for flu or herpes. Before a T cell encounters its particular bug, it is said to be "naive." When a naive cell comes into contact with its germ, explains immune system expert Clifford Lane, "it sort of says, 'Oh my God, I've waited my whole life for this moment!' " It starts dividing, creating a massive progeny of "activated" T cells, which in turn orchestrate the immune system's complex response. After the infection has been cleared, the activated cells remain in the body. Indeed, they are called "memory" cells, because they are able to "remember" the germ and can mobilize very quickly to fight it off again.

Researchers have feared that HIV might kill all the T cells for certain diseases, leaving the immune system unable to recognize them. In the lingo of immunologists, there would be holes in the immune "repertoire." If so, a person might suppress HIV, but still be vulnerable to opportunistic infections.

That's why researchers have been especially concerned about naive cells. If new ones could be generated, they might fill the gaps in the tattered immune repertoire. But if HIV decimates naive cells, a patient might be able to recognize only those diseases his or her immune system remembers. If such patients encountered a germ for the first time, they might have no defense.

What Autran saw is that, after at least six months of effective therapy, cells that seem to be naive rose markedly in all her patients. At the conference, two other teams independently reported the same phenomenon.

The next big question is whether naive cells really are naive. Some scientists doubt it, because such cells are believed to be generated only in the thymus. Even in uninfected people, the thymus essentially shuts down by age 20, its job having been completed in childhood. And, says veteran researcher Anthony Fauci, autopsies show that "HIV destroys the thymus."

But that destruction might happen only at the end stage of AIDS, along with the wholesale wreckage of the lymph nodes, another key immune-system site. One research team found that when lymph tissue has severely deteriorated, the potent new AIDS drugs work for only a short time. But, if therapy begins when the lymph tissue is relatively healthy, some of the damage might be reversible. At two "late-breaker" sessions, researchers tentatively reported signs of possible improvement in lymph biopsies after months of effective therapy: the tissue, said one researcher, looked "less ratty."

Most likely, the immune system will never recover to pre-HIV levels. But it might not need to. It may be sufficient to achieve the first two phases of immune recovery: the initial increase in T cells, and a downshifting of the immune system from its overheated, anti-HIV state. Indeed, if the drugs work, most patients quickly get much better. Researchers reported dramatic turnarounds: even the most dreaded of AIDS diseases—PML, which causes lesions in the brain and is incurable—healed in some patients.

Such remissions appear to be happening on a wide scale. In one of the conference's most widely heralded findings, New York City reported a steep decline in deaths, coinciding with the advent of the new protease inhibitors. Researchers from France and Los Angeles also reported fewer AIDS-related deaths, illnesses, and hospitalizations. "Even if the immune system just comes back to a minimal level," says Autran, "we don't need to be pessimistic."

On the other hand, it's possible that the general declines in illness and death will turn out to be temporary. Doctors strongly caution patients to continue their prophylaxis against the big AIDS killers, such as Pneumocystis pneumonia and CMV, even if their immune systems seem to be recovering. And they practically beg their patients to stick to the demanding protease inhibitor regimens, which can exceed 20 pills a day. In one sobering presentation, researchers described a patient who stopped taking his medicine for just one week: Even though his drugs had pinned down HIV for nine months, that week was all HIV needed to thoroughly re-seed his lymph tissue.

Still, if patients can keep taking their pills, and those pills keep working, there's reason to hope the immune system can make a comeback. ❖

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